REMARKS/ARGUMENTS

The foregoing amendments in the specification and claims are of formal nature, and do not add new matter.

Prior to the present amendment, Claims 28-33 were pending in this application. With this amendment, Claim 33 have been canceled without prejudice, and Claim 28 has been amended to clarify what Applicants have always regarded as their invention.

Claims 28-32 are pending after entry of the instant amendment. Applicants expressly reserve the right to pursue any canceled matter in subsequent continuation, divisional or continuation-in-part applications.

1. Formal Matters

Applicants thank the Examiner for entering the Preliminary Amendments filed on December 6, 2001 and August 29, 2002 into the record. Applicants further thank the Examiner for entering the Information Disclosure Statement filed on October 30, 2002 and March 6, 2002 into the record.

2. Priority

The Examiner states that due to the excessive number of applications from which the present application claims benefit, priority cannot be determined.

The Examiner's attention is respectfully directed to the Preliminary Amendment filed on August 29, 2002, which states that the present application is "a continuation of, and claims priority under 35 U.S.C. §120 to, U.S. Application 09/946,374 filed 9/4/2001, which is a continuation of, and claims priority under 35 U.S.C. §120 to, PCT Application PCT/US00/04342 filed 2/18/2000, which is a continuation-in-part of, and claims priority under 35 U.S.C. §120 to, U.S. Application 09/403,297 filed 10/18/1999, now abandoned, which is the National Stage filed under 35 U.S.C. §371 of PCT Application PCT/US99/20111 filed 9/1/1999, which claims priority under 35 U.S.C. §119 to U.S. Provisional Application 60/100,627 filed 9/16/1998."

As discussed below, Applicants rely on the chondrocyte proliferation assay (Example 153, Assay #111) for patentable utility which was first disclosed in PCT Application

PCT/US00/04342 filed on February 18, 2000, priority to which has been claimed in this application. Accordingly, the present application is entitled to at least the February 18, 2000 priority. In support, Applicants enclose herewith page 525 of the PCT Publication WO 00/78961, corresponding to PCT Application PCT/US00/04342.

3. Information Disclosure Statement

In response to the Examiner's assertion that references 7 and 8 in the Information Disclosure Statement filed on October 30, 2002 are not in proper format, Applicants file herewith, an Information Disclosure Statement listing each reference of the "Blast Search" separately and including authors/inventors, relevant accession numbers and publication dates. Applicants respectfully request that the listed information be considered by the Examiner and be made of record in the above-identified application.

4. Specification

As requested by the Examiner, the specification has been amended to remove embedded hyperlink and/or other form of browser-executable code. In addition, the title of the application has been amended to recite a new, descriptive title indicative of the invention to which the claims are directed.

Further, Applicants have amended the specification to clearly recite the conditions of the deposits made under the Budapest Treaty.

5. Claim Objections

Claims 28-33 were objected to for reciting a Figure number and a SEQ ID NO. Applicants submit that the cancellation of Claim 33 renders the objection to these claims moot. Further, Applicants submit that Claim 28 has been amended to only recite SEQ ID NO. Accordingly, Applicants respectfully request that the Examiner withdraw its objection to Claims 28-32.

6. **Claim Rejections Under 35 U.S.C. §112, Second Paragraph**

A. Claim 31 is rejected under et U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner alleges that it is not understood "how an antibody can be both an 'antibody' and a 'fragment'."

Applicants submit that the definition of "antibody," provided on page 308, line 22 onwards, includes "antibody fragments". As the Examiner is aware, Applicants can be their own lexicographer and hence Claim 31 is definite and this rejection should be withdrawn.

B. The Examiner also alleges that Claim 33 is confusing "since it is not clear what the definition of 'specifically binds' is."

Without acquiescing to the propriety of this rejection and solely in the interest of expedited prosecution in this case, Applicants have canceled Claim 33 and have amended Claim 28 (and, as a consequence, those claims dependent from the same) to recite "specifically binds." Applicants respectfully submit that the art-recognized meaning of "specific" binding is that the antibody that specifically binds to a particular antigen does not significantly cross-react with another antigen. Therefore, the term "specifically binds" in Claim 28 (and, as a consequence, those claims dependent from the same) clearly refers to an antibody that is able to bind to the PRO1347 polypeptide without significantly cross reacting with another antigen. Accordingly, one skilled in the art would exactly know what the scope of the invention is, and the present rejection should be withdrawn.

Claim Rejections Under 35 U.S.C. §103

Claims 28-33 are rejected un 35 U.S.C. §103(a) as being unpatentable over Shibui *et al* in view of Lai *et al.*. The Examiner asserts that "Shibui *et al.* teach a protein which is 54.1% identical to SEQ ID NO:148 of the present invention. Shibui do not teach antibodies. However, Lai teach humanized antibodies ... monoclonal antibodies... and labeled antibodies. Therefore, the Examiner alleges that "[i[t would have been obvious to one skilled in the art at the time of the present invention to have made humanized, labeled, and monoclonal antibodies to the protein of

Shibui for the purpose of diagnostic (label) as well as for treatment of human diseases (humanized)."

Applicants respectfully disagree and traverse this rejection.

Applicants submit that the cancellation of Claim 33 renders the objection to these claims moot.

As the Examiner is aware, to establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). *See* M.P.E.P. 2143.03.

The test for obviousness is whether the prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention. In re Deuel 51 F.3d 1552, 1558, 34 USPQ2d 1210, 1215 (Fed. Cir. 1995).

> A prior art disclosure of the amino acid sequence of a protein does not necessarily render particular DNA molecules encoding the protein obvious because the redundancy of the genetic code permits one to hypothesize an enormous number of DNA sequences coding for the protein. No particular one of these DNA's can be obvious unless there is something in the prior art to read to the particular DNA and indicate that it should be prepared.

As discussed above, Applicants have amended Claim 28(and, as a consequence, those claims dependent from the same) to recite "an antibody that specifically binds to the polypeptide of SEQ ID NO:148." Therefore, Claim 28 (and, as a consequence, those claims dependent from the same) clearly refers to an antibody that is able to bind to the PRO1347 polypeptide *without* significantly cross reacting with another antigen, including the sequence disclosed in Shibui *et al.*

Further, the Examiner admits that the protein sequence of Shibui is only 54.1% identical to SEQ ID NO:148 of the present application. In view of this limited degree of sequence identity, the PRO1347 polypeptide is not obvious over the sequence of Shibui et al. This is indirectly acknowledged by the fact that the Examiner did not reject the polypeptide claims over Shibui et al. in parallel application U.S. Application 10/006,172. Accordingly, antibodies that bind to SEQ ID NO: 148 are not rendered obvious by the sequence disclosed in Shibui either, absent some teaching or suggestion in the art, or in the cited reference itself, to change the amino acid sequence of Shibui so it would specifically bind to the anti-PRO1347 antibodies. Since such teaching or suggestion is entirely missing, the combination of Shibui *et al.* with Lai does not make the pending claims obvious. Thus, Applicants respectfully request the reconsideration and withdrawal of the present rejection.

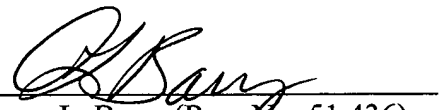
CONCLUSION

All claims pending in the present application are believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for an extension of time, or credit overpayment to Deposit Account No. **08-1641** (Attorney's Docket No. **39780-2830 P1C12**). Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: October 6, 2004

By: 
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BUDAPEST TREATY ON THE INTERNATIONAL RECOGNITION OF
THE DEPOSIT OF MICROORGANISMS FOR THE PURPOSES OF PATENT PROCEDURE

INTERNATIONAL FORM

RECEIPT IN THE CASE OF AN ORIGINAL DEPOSIT ISSUED PURSUANT TO RULE 7.3
AND VIABILITY STATEMENT ISSUED PURSUANT TO RULE 10.2

To: (Name and Address of Depositor or Attorney)

Genentech, Inc.
Attn: Ginger R. Dreger
1 DNA Way
South San Francisco, CA 94080-4990

Deposited on Behalf of: Genentech, Inc.

Identification Reference by Depositor:	**ATCC Designation**
pRK5E-based plasmid DNA64952-1568 (Ref. PR1568)	203222
pINCY-based plasmid DNA64903-1553 (Ref. PR1553)	203223
pRK5D-based plasmid DNA64950-1590 (Ref. PR1590)	203224
pINCY-based plasmid DNA66521-1583 (Ref. PR1583)	203225
pBlue-based plasmid DNA66520-1536 (Ref. PR1536)	203226
pRK5B-based plasmid DNA65423-1595 (Ref. PR1595)	203227

The deposits were accompanied by: ___ a scientific description _ a proposed taxonomic description indicated above. The deposits were received September 15, 1998 by this International Depository Authority and have been accepted.

AT YOUR REQUEST: X We will not inform you of requests for the strains.

The strains will be made available if a patent office signatory to the Budapest Treaty certifies one's right to receive, or if a U.S. Patent is issued citing the strains, and ATCC is instructed by the United States Patent & Trademark Office or the depositor to release said strains.

If the cultures should die or be destroyed during the effective term of the deposit, it shall be your responsibility to replace them with living cultures of the same.

The strains will be maintained for a period of at least 30 years from date of deposit, or five years after the most recent request for a sample, whichever is longer. The United States and many other countries are signatory to the Budapest Treaty.

The viability of the cultures cited above was tested October 2, 1998 On that date, the cultures were viable.

International Depository Authority: American Type Culture Collection, Manassas, VA 20110-2209 USA.

Signature of person having authority to represent ATCC:

Barbara M. Hailey

Barbara M. Hailey, Administrator, Patent Depository

Date: October 7, 1998

EXAMPLE 152: Proliferation of Rat Utricular Supporting Cells (Assay 54)

This assay shows that certain polypeptides of the invention act as potent mitogens for inner ear supporting cells which are auditory hair cell progenitors and, therefore, are useful for inducing the regeneration of auditory hair cells and treating hearing loss in mammals. The assay is performed as follows. Rat UEC-4 utricular epithelial cells are aliquoted into 96 well plates with a density of 3000 cells/well in 200 μl of serum-containing medium at 33°C. The cells are cultured overnight and are then switched to serum-free medium at 37°C. Various dilutions of PRO polypeptides (or nothing for a control) are then added to the cultures and the cells are incubated for 24 hours. After the 24 hour incubation, ^{3}H-thymidine (1 μCi/well) is added and the cells are then cultured for an additional 24 hours. The cultures are then washed to remove unincorporated radiolabel, the cells harvested and Cpm per well determined. Cpm of at least 30% or greater in the PRO polypeptide treated cultures as compared to the control cultures is considered a positive in the assay.

The following polypeptides tested positive in this assay: PRO1340.

EXAMPLE 153: Chondrocyte Proliferation Assay (Assay 111)

This assay is designed to determine whether PRO polypeptides of the present invention show the ability to induce the proliferation and/or redifferentiation of chondrocytes in culture. PRO polypeptides testing positive in this assay would be expected to be useful for the therapeutic treatment of various bone and/or cartilage disorders such as, for example, sports injuries and arthritis.

Porcine chondrocytes are isolated by overnight collagenase digestion of articular cartilage of the metacarpophalangeal joint of 4-6 month old female pigs. The isolated cells are then seeded at 25,000 cells/cm^2 in Ham F-12 containing 10% FBS and 4 μg/ml gentamycin. The culture media is changed every third day and the cells are reseeded to 25,000 cells/cm^2 every five days. On day 12, the cells are seeded in 96 well plates at 5,000 cells/well in 100μl of the same media without serum and 100 μl of either serum-free medium (negative control), staurosporin (final concentration of 5 nM; positive control) or the test PRO polypeptide are added to give a final volume of 200 μl/well. After 5 days at 37°C, 20 μl of Alamar blue is added to each well and the plates are incubated for an additional 3 hours at 37°C. The fluorescence is then measured in each well (Ex:530 nm; Em: 590 nm). The fluorescence of a plate containing 200 μl of the serum-free medium is measured to obtain the background. A positive result in the assay is obtained when the fluorescence of the PRO polypeptide treated sample is more like that of the positive control than the negative control.

The following PRO polypeptides tested positive in this assay: PRO1265, PRO1412, PRO1347, PRO1279, PRO1410 and PRO1474.

EXAMPLE 154: Inhibition of Heart Neonatal Hypertrophy Induced by LIF+ET-1 (Assay 74)

This assay is designed to determine whether PRO polypeptides of the present invention show the ability to inhibit neonatal heart hypertrophy induced by LIF and endothelin-1 (ET-1). A test compound that provides a positive response in the present assay would be useful for the therapeutic treatment of cardiac insufficiency diseases or disorders characterized or associated with an undesired hypertrophy of the cardiac muscle.

Cardiac myocytes from 1-day old Harlan Sprague Dawley rats (180 μl at 7.5 x 10^4/ml, serum <0.1, freshly isolated) are introduced on day 1 to 96-well plates previously coated with DMEM/F12 + 4%FCS. Test